



Iodine supplementation during pregnancy of hypothyroid women treated with L-thyroxine neither influences neonatal TSH nor prevents decrease in maternal free thyroid hormone concentrations in second and third trimesters

Suplementacja jodowa u ciężarnych z niedoczynnością tarczycy leczonych L-tyroksyną nie wpływa na stężenia TSH noworodków ani nie zapobiega obniżeniu stężeń wolnych hormonów tarczycy u matek w drugim i trzecim trymestrze

Helena Jastrzębska¹, Magdalena Kochman¹, Zbigniew Bartoszewicz²,
Mariusz Ołtarzewski³, Romuald Dębski⁴, Wojciech Zgliczyński¹

¹Department of Endocrinology, Centre of Postgraduate Medical Education, Bielanski Hospital, Warsaw, Poland

²Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland

³Institute of Mother's and Child's Health, Warsaw, Poland

⁴Department of Obstetrics and Gynaecology, Centre of Postgraduate Medical Education, Bielanski Hospital, Warsaw, Poland

Abstract

Introduction: Pregnant women require about 250 µg of iodine daily. Hypothyroid women treated with L-thyroxine do not utilise iodine, and metabolism of L-thyroxine tablets is an additional source of iodine for their foetuses.

The aim of the study was to evaluate the influence of iodine supplementation in hypothyroid pregnant women treated with L-thyroxine on neonate TSH concentration and maternal thyroid parameters.

Material and methods: Ninety-two pregnant women with primary hypothyroidism on adequate thyroid hormone replacement were voluntarily divided into two groups: "thyroxine" (n = 38) treated with L-thyroxine only, and "thyroxine + iodine" (n = 54) treated additionally with 150 µg/day of iodine since 10th gestational week.

Primary outcomes were the maternal thyroid function tests (TSH, fT4, fT3) and neonatal TSH concentrations at the 3–4th day of life. Urinary iodine concentration was measured at first and third trimester to compare iodine status in both groups.

Results: Iodine supplementation significantly increased median urinary ioduria in the third trimester (from 95.15 µg/L to 151.50 µg/L), but did not prevent the decrease of maternal fT4 and fT3 concentrations in the second and third trimester. Median neonate TSH concentration in both groups was within normal range, but was 33% higher in the "thyroxine + iodine" than in the "thyroxine" group (1.91 mIU/L vs. 1.34 mIU/L). Moreover, 8.77% of newborns in the "thyroxine + iodine" group had TSH > 5 mIU/L.

Conclusions: We did not find evidence for a positive influence of iodine supplementation on thyroid function of either hypothyroid pregnant women sufficiently treated with L-thyroxine or their neonates. (*Endokrynol Pol* 2016; 67 (4): 367–374)

Key words: pregnancy; hypothyroidism; iodine supplementation; neonatal TSH; ioduria

Streszczenie

Wstęp: U ciężarnych rekomendowana jest zwiększona podaż jodu pokrywająca zapotrzebowanie kobiety i dziecka. Tarczycza ciężarnej z niedoczynnością nie zużywa jodu. Jod dostarczony w diecie, suplementach oraz pochodzący z metabolizmu tyroksyny stanowi źródło wyłącznie dla płodu.

Celem pracy była ocena wpływu suplementacji jodowej u ciężarnych z niedoczynnością tarczycy na stężenia TSH noworodków i parametry tarczycowe matek.

Materiał i metody: Badanie przeprowadzono w grupie 92 ciężarnych z pierwotną niedoczynnością tarczycy wyrównaną w trakcie leczenia L-tyroksyną podzielono na dwie grupy: „tyroksyna” (n = 38) leczone jedynie tyroksyną i „tyroksyna + jod” (n = 54) otrzymujące tyroksynę i od 10. tygodnia ciąży jod 150 µg/dobę.

U matek oznaczano TSH, fT4, fT3 w każdym trymestrze a u noworodków TSH w 3–4 dobie życia. Zaopatrzenie w jod oceniano na podstawie jodurii badanej w 1. i 3. trymestrze.

Wyniki: Suplementacja jodowa spowodowała istotne zwiększenie mediany jodurii z 95,15 µg/l do 151,50 µg/l, jednak nie zapobiegła obniżeniu stężeń fT4 i fT3 w 2. i 3. trymestrze. W obu grupach mediana stężeń TSH noworodków utrzymywała się w granicach normy, ale była o 33% wyższa w grupie „tyroksyna + jod” niż w grupie „tyroksyna” (1,91 mIU/l vs. 1,34 mIU/l). Tylko w grupie „tyroksyna + jod” stwierdzono u noworodków stężenie TSH > 5 mIU/l co dotyczyło 8,77% badanych.

Wnioski: Nie uzyskano dowodów na pozytywny wpływ suplementacji jodowej u ciężarnych z niedoczynnością tarczycy właściwie wyrównanych L-tyroksyną na TSH noworodków. Nie zaznaczył się także wpływ na parametry tarczycowe u kobiety ciężarnej.

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Słowa kluczowe: ciąża; niedoczynność tarczycy; suplementacja jodowa; TSH noworodków; joduria



Helena Jastrzębska M.D., Ph.D., Department of Endocrinology, Centre of Postgraduate Medical Education, Bielanski Hospital, Ceglowska 80, 01-809 Warsaw, Poland, phone/fax: + 48 22 834 31 31, e-mail: hjastrzebska@cmkp.edu.pl

Introduction

Iodine deficiency during pregnancy may result in insufficient maternal and foetal thyroid hormone synthesis and may lead to impaired brain development of the child [1]. On the other hand, iodine excess may inhibit foetal thyroid, which begins to synthesise thyroid hormones at about the 10th week of pregnancy [2], causing hypothyroidism and goitre [3].

The assessment of iodine intake in the population can be made using urinary iodine concentration and indirectly by measurement of TSH concentration in neonates [4]. According to WHO experts, the median urinary iodine concentration in pregnant women is between 150 and 249 $\mu\text{g/L}$, and a percentage of neonates in their 3rd–4th day of life with TSH level higher than 5 mU/L below 3% indicates adequate iodine intake [5].

With reference to increased dietary iodine requirements during pregnancy, WHO/UNICEF/ICCIDD recommend a daily iodine intake during pregnancy of 200 to 300 μg , mean 250 μg , maximally 500 μg [4]. Therefore, to ensure an adequate iodine supply for the mother and her child in many European countries pregnant and breastfeeding women are advised to receive an additional daily oral dose of 100–200 μg of potassium iodide. There is no separate recommendation for hypothyroid women in whom the thyroid gland is not able to synthesise hormones and who are treated with L-thyroxine. In these cases, not only iodine provided with food and released during metabolism of maternal hormones, but also iodine derived from L-thyroxine tablets remains at the disposal of the child's thyroid [6]. Following the metabolism of 100 μg of L-thyroxine, about 60 μg of iodine is released, which, together with the dietary iodine intake pool, remains at the disposal of the thyroid of the child [6]. The neonate thyroid hormone synthesis begins at about the 10th week of pregnancy. To the best of our knowledge, there are no data available regarding iodine supplementation in pregnant hypothyroid women treated with substitutive doses of L-thyroxine. Thus, we aimed to estimate the influence of iodine supplementation in hypothyroid pregnant women receiving L-thyroxine on their thyroid status evaluated by measurement of TSH, fT3, and fT4 concentrations, as well as on the thyroid function of their newborns assessed by neonate TSH concentration.

Material and methods

Subjects

The study population included 96 pregnant Caucasian women with a history of primary hypothyroidism. All participants were consecutively recruited from a single

endocrinology outpatient clinic. The study lasted from 2008 until 2013.

Ninety-two patients completed the study because there were two miscarriages at the 12th week of gestation, one missed abortion at the 26th weeks of gestation, and one missed data collection due to refusal to continue the study.

Seventeen of the patients were treated because of subclinical hypothyroidism, in all cases caused by Hashimoto disease. All patients were physically examined and had TSH, fT3, and fT4 concentrations measured every 4–6 weeks. They were on a standard diet and were treated with L-thyroxine only before pregnancy and until the end of the 10th week of gestation. Thereafter, the studied group was divided into two subgroups: the “thyroxine” group, consisting of 38 subjects who continued with appropriate dose of L-thyroxine only; and the “thyroxine + iodine” group — 54 subjects who additionally to L-thyroxine received a standard dose of 150 μg iodine daily as potassium iodide in a separate pill. Commercially available multivitamin and mineral supplements were not used. The enrolment to subgroups was made on a voluntary basis. The basic characteristics of the subgroups are presented in Table I.

During pregnancy and perinatal period the women were not exposed to the iodinated contrast media, thyroid affecting medications, iodinated antiseptics, or cigarette smoking.

The study protocol was reviewed and approved by the Ethics Committee of the Centre of Postgraduate Medical Education in Warsaw, Poland. Signed informed consent form was obtained from all patients.

Analytical methods

Mothers' blood TSH, free T3 (fT3), and free T4 (fT4) concentrations in samples collected at 8–10, 22–24, and 34–36 weeks of pregnancy were used for statistical analysis, the first and third of them corresponding to the urinary iodine excretion measurements. To avoid confounding factors, the samples were taken in the morning before L-thyroxine as well as iodine ingestion. Serum was separated by centrifugation and the hormone concentration was assayed immediately.

Quantitative analyses of TSH, fT3, and fT4 were performed by a chemiluminescent immunoassay (EURO/DPC, UK) using an Immulite 2000 automatic analyser. The manufacturer's reference ranges for non-pregnant adult in these kits were as follows: TSH 0.4–4.0 mIU/L (sensitivity 0.004 mIU/L, intra-assay coefficient of variance — CV 3.8–12.5%), fT4 11.5–22.7 pmol/L (sensitivity 3.2 pmol/L, intra-assay CV 3.0–7.8%), and fT3 1.8–4.2 pg/mL (sensitivity 1.0 pg/mL, intra-assay CV 4.3–9.1%), respectively.

Table I. Basic characteristics of the studied groups
Tabela I. Podstawowa charakterystyka badanych grup

Parameters	"Thyroxine" group	"Thyroxine + iodine" group
Number of patients	38	54
Aetiology of hypothyroidism:		
Hashimoto's thyroiditis	31	46
Thyroidectomy propter nodular thyroid disease	2	2
Thyroidectomy propter Graves' disease	1	1
Thyroidectomy and radioiodine therapy propter thyroid cancer	0	1
Thyroidectomy, radioiodine and external radiotherapy propter thyroid cancer	1	0
Radioiodine therapy propter Graves' disease	2	4
Thyroidectomy and radioiodine therapy propter Graves' disease and thyroid cancer	1	0
Severity of hypothyroidism		
overt	27	46
subclinical	9	8
Coexisting disorders:		
Celiac disease	1	0
Pernicious anaemia	1	0
Hypoparathyroidism	1	0
Diabetes type 1	0	1
Conception:		
Natural	38	47
In vitro fertilisation	0	6
Insemination	0	1
Age (years) mean \pm SD	30.16 \pm 3.5	30.10 \pm 3.53

Urinary iodine excretion was evaluated in every subject in the 1st and 3rd trimester of pregnancy. Taking into account the high diurnal and day-to-day variability of urinary iodine excretion, we assessed urinary iodine concentration for every pregnant subject four times: twice at the 10th week of gestation and twice at the 34th-36th week of gestation. It was measured in a spot of morning urine sample by the catalytic cerium/arsenic method based on the Sandell-Kolthoff reaction, which was preceded by alkaline ashing [7]. TSH concentration in neonates was evaluated as a part of the neonatal screening protocol. The procedure is based on determination of TSH by a two-site IRMA method in dried blood spots obtained by the heel puncture at the 3rd-4th day of life. In Poland, values \geq 15 mIU/L in whole blood are considered abnormal and require further assessment for congenital hypothyroidism.

Statistical analyses

Statistical analyses were performed using STATISTICA 9.0 PL.

The Kolmogorov-Smirnov test was used to estimate the normal distribution of evaluated parameters. The

Student t test was used for normally distributed data, while Wilcoxon-matched-paired test and the Bonferoni-Holm adjustment were used for data not normally distributed. The Spearman test was performed to calculate the correlations between groups. The values were reported as median, minimum, and maximum. Statistical significance was accepted at $P < 0.05$.

Results

All women remained euthyroid throughout pregnancy, and that fact was confirmed by serum TSH level, adopted as a concentration above 0.4 mIU/L and below 2.5 mIU/L. Their serum fT4 and fT3 concentrations remained within normal range for the general population.

Median urinary iodine concentration at the 10th week of pregnancy was below the optimal range for pregnant women both in the "thyroxine" and "thyroxine + iodine" groups (median \pm IQR: 83.15 \pm 41.03 μ g/L and 95.15 \pm 69.45 μ g/L, respectively), which indicated mild iodine deficiency according to the WHO criteria (Fig. 1). In the first trimester, only 5 of 38 women of the "thyroxine" group and 11 of 54 patients of the

Table II. Selected parameters in pregnant hypothyroid women and their offspring
Tabela II. Wybrane parametry u kobiet ciężarnych z niedoczynnością tarczycy i ich dzieci

Patient	Parameter	"Thyroxine" group	"Thyroxine + iodine" group	p
Time of examination				
Mother First trimester	Thyroxine dose [$\mu\text{g}/\text{d}$]			
	mean \pm SD	86.40 \pm 44.60	83.142 \pm 38.32	ns
	range	50–200	50–175	
	Thyroxine dose [$\mu\text{g}/\text{kg}/\text{d}$]			
	mean \pm SD	1.38 \pm 0.46	1.40 \pm 0.69	ns
	range	0.51–2.21	0.62–3.12	
Mother Third trimester	Urinary iodine excretion [$\mu\text{g}/\text{L}$]			
	Median \pm IQR	83.15 \pm 41.03	95.15 \pm 69.45	ns
Mother Third trimester	Thyroxine dose [$\mu\text{g}/\text{d}$]			
	mean \pm SD	119.0 \pm 51.59	100.0 \pm 41.62	ns
	range	75–200	100–200	
	Thyroxine dose [$\mu\text{g}/\text{kg}/\text{d}$]			
	mean \pm SD	1.57 \pm 0.48	1.50 \pm 0.58	ns
	range	0.89–2.564	0.89–2.86	
Neonate 3–4 days after birth	Urinary iodine excretion [$\mu\text{g}/\text{L}$]			
	Median \pm IQR	101.09 \pm 81.66	151.50 \pm 80.77	< 0.01
Neonate 3–4 days after birth	TSH [mIU/L]			
	Median \pm IQR	1.34 \pm 2.21	1.91 \pm 2.41	ns
	range	0.01–3.86	0.01–9.48	
	Number (percentage) of newborns with TSH > 5mIU/L	0	5/57 (8.77%)	

ns — non-significant

"thyroxine and iodine" group had adequate urinary iodine excretion (Fig. 2). Introduction of iodine supplementation in the "thyroxine + iodine" group resulted in a significant increase of median urinary iodine concentration at the 3rd trimester up to 151.50 \pm 80.77 $\mu\text{g}/\text{L}$ ($p < 0.001$), while in the "thyroxine" group the median urinary iodine excretion did not change and remained low (101.09 \pm 81.66 $\mu\text{g}/\text{L}$). The percentage of individuals with urinary iodine concentration over 150 $\mu\text{g}/\text{L}$ in the "thyroxine + iodine" group increased significantly but remained steady in the group treated with thyroxine alone (Fig. 2).

In both groups, serum fT4 concentrations significantly decreased in the second and third trimester when compared with the first. In the "thyroxine + iodine" group, TSH and fT3 levels were also significantly lower in the third trimester when compared with the first (Fig. 1). TSH and fT3 concentrations did not differ between the "thyroxine" and "thyroxine + iodine" groups in any trimester, while fT4 level was lower in the third trimester in the "thyroxine + iodine" group.

TSH concentrations were analysed in 39 neonates in the "thyroxine" group and 57 in the "thyroxine + iodine" group (as one of the triplets died in the first day of life) (Table III). The neonate TSH concentrations both in the "thyroxine" and the "thyroxine + iodine" groups were within the normal range with median TSH level of 1.34 mIU/L and 1.91 mIU/L, respectively, and did not differ between the groups. The newborn TSH concentration above 5 mIU/L was found in five neonates (5.11, 5.33, 5.66, 7.38, and 9.26 mIU/L, respectively). Interestingly, all of those children were from mothers of the "thyroxine + iodine" group (5/57 = 8.77%), who were treated because of overt hypothyroidism (four of them due to Hashimoto's thyroiditis and one — after strumectomy propter nodular goitre) (Table II). One child with TSH concentration of 5.66 mIU/L had a twin brother in whom the TSH level was found to be 0.5 mIU/L. Duration of pregnancy did not differ in both groups and was 37.68 weeks and 39.0 weeks, respectively. The prevalence of gestational diabetes was similar in both groups and remained within the aver-

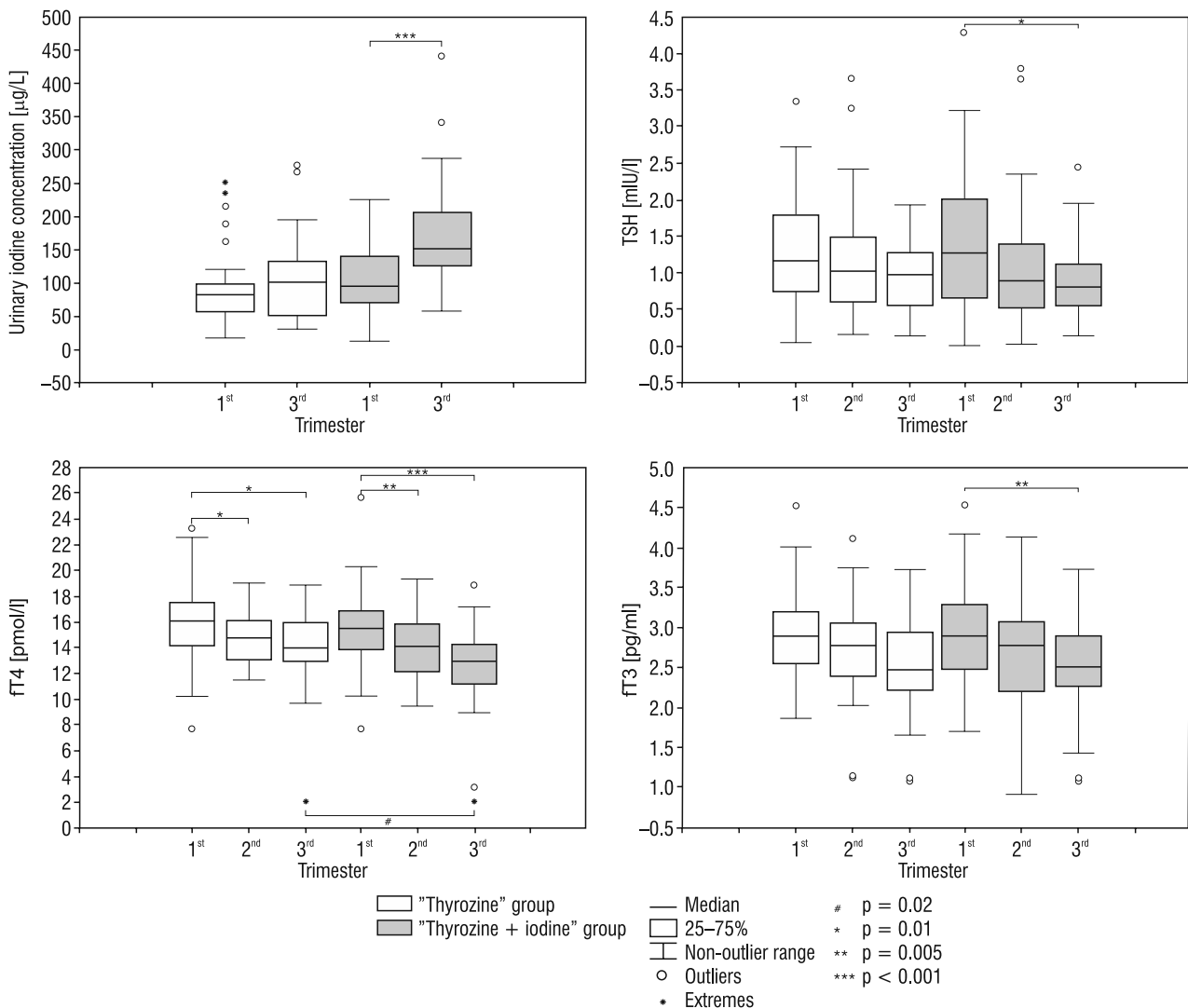


Figure 1. Evolution of urinary iodine, TSH, fT4, and fT3 concentrations in hypothyroid women treated with thyroxine alone or with thyroxine and iodine at each trimester of pregnancy. Data are presented as median \pm IQR. Significant differences in urinary iodine excretion as well as TSH, fT4, and fT3 concentrations between the trimesters in each of the two groups are shown in the diagrams

Rycina 1. Zmiany stężeń jodu w moczu porannym oraz TSH, fT4 i fT3 w poszczególnych trymestrach ciąży u ciężarnych z niedoczynnością tarczycy leczonych samą L-tyroksyną lub L-tyroksyną i preparatem jodu. Dane przedstawione jako mediana \pm IQR. Na wykresach zaznaczono istotne różnice w jodurii oraz stężeniach TSH, fT4 i fT3 pomiędzy poszczególnymi trymestrami w obu badanych grupach

age range (below 10%) for pregnant women (Table III). Perinatal complications occurred in two cases from the "thyroxine" group. One patient developed sclerosis multiplex and another one suffered an ischaemic stroke with left-sided hemiplegia. In this particular case previously undiagnosed foramen in atrial septum was found thereafter.

Discussion

There are four parameters recommended for the assessment of iodine status in human populations: urinary iodine concentration, goitre rate in school-age children, thyroglobulin concentration, and neonatal

TSH concentration [2]. Urinary iodine concentration is a sensitive indicator of a recent, daily iodine intake. Thyroglobulin concentration indicates iodine supply during the preceding weeks to months, whereas thyroid volume corresponds to long-term iodine nutrition lasting months to years [2]. Neonatal TSH is a marker of iodine supply during late foetal life.

We found it reasonable to question whether standard iodine supplementation in hypothyroid pregnant women on adequate thyroid hormone replacement influence thyroid function of their neonates. In Poland an iodine prophylaxis program has been implemented since 1997, with modification in 2010, which includes mandatory iodisation of household salt with

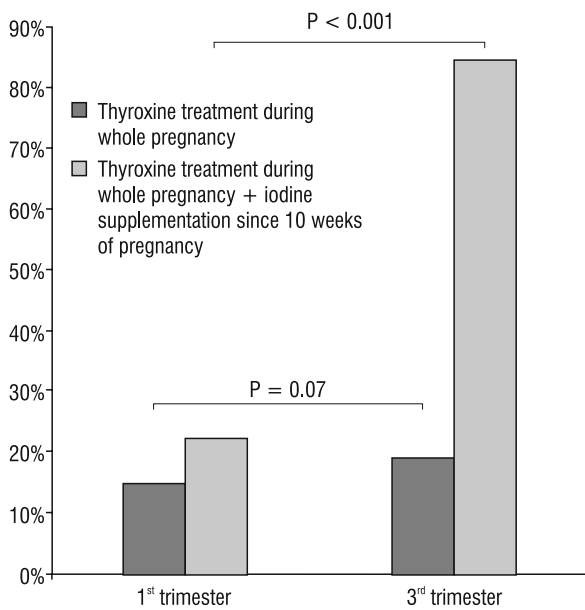


Figure 2. Percentage of hypothyroid pregnant women treated with thyroxine or thyroxine + iodine with urinary iodine excretion over 150 µg/L

Rycina 2. Odsetek kobiet z jodurią powyżej 150µg/l w grupie ciężarnych z niedoczynnością tarczycy leczonych samą L-tyroksyną oraz w grupie leczonych L-tyroksyną i preparatem jodu

Table III. The course and outcome of pregnancy

Tabela III. Przebieg ciąży i porodu

	"Thyroxine" group	"Thyroxine + iodine" group
Number of women	38	54
Gestational diabetes therapy	2 (5.26%)	3 (5.56%)
	2 — diet	2 — diet, 1 — diet + insulin
Multiple pregnancies	1 (2.63%)	3 (5.56%)
number of infants	2 (twins)	7 (2 twins, 1 triplets)
Mode of delivery		
vaginal	36 (94.73%)	49 (90.74%)
caesarean	2 (5.26%)	5 (9.25%)
Pre-term delivery	1 (2.6%)	4 (7.4%)
Week of pregnancy at childbirth ^a	37.68 ± 6.07 (36-41)	39.0 ± 1.48 (27-41)
Number of neonates	39	58

a — mean ± SD (range)

30 ± 10 mg KI/kg salt or 39 ± 13 mg KIO₃/kg salt and supplementation of pregnant and breastfeeding women with an additional 150 µg of iodine daily [8]. Despite the

fact that Poland in 2003 was considered by the WHO, UNICEF, and ICCIDD to be a country with sufficient iodine supply [9], we did not find satisfactory urinary iodine concentrations in the group under study. Median ioduria at the first trimester of gestation in hypothyroid women being efficiently treated with L-thyroxine was 85.28 µg/L, which corresponds to the epidemiological criteria of insufficient iodine supply [10]. Before introducing iodine supplementation only 17.4% of our population of 94 subjects had urinary iodine concentration above 150 µg/L. Iodine supplementation resulted in an expected increase in median morning ioduria, as well as an increase in the percentage of patients with desirable urinary iodine concentration above 150 µg/L to 61.1%. We realise that the number of participants in our study is not adequate to assess iodine sufficiency in the population [11]; however, the increase in iodine urinary excretion confirms additional iodine intake in the "thyroxine + iodine" group.

In healthy pregnant women fT4 concentrations decrease at the second and third trimester [12]. This phenomenon was considered to be a result of changes in thyroxine-binding globulin and albumin concentrations [13, 14] or of a true hypothyroxinaemia, possibly reflecting iodine deficiency [15]. Brucker et al. reported in women with normal thyroid function a drop of both fT4 and fT3 levels after the first trimester of pregnancy, with no influence of iodine supplementation [16]. Similarly, in our material of hypothyroid women treated with L-thyroxine, we observed a significant decrease of fT4 levels during pregnancy irrespectively of iodine supplementation, which was not accompanied by an increase in TSH concentration. Moreover, fT4 was significantly lower in the "thyroxine + iodine" than in the "thyroxine" group. The concentration of fT3 decreased significantly in the "thyroxine + iodine" group only; however, a similar tendency was seen in the "thyroxine" group (Fig. 1). Our results seem to confirm that a drop in fT4 and fT3 levels at second and third trimester is a physiological phenomenon in pregnancy and not a consequence of iodine deficiency.

Proper iodine supply ensures normal thyroid function of the child, which is essential for its somatic and neurological development [1, 17]. Neonatal TSH is an important marker of iodine supply during later gestation, as its concentration correlates with the thyroid hormone level of the foetus [1]. Insufficient supply of iodine leads to depletion of thyroid hormone production and consequently to overstimulation of the thyroid gland by TSH [18]. However, whether newborn TSH measured in 3–4 days after birth is a sensitive indicator of mild iodine deficiency during pregnancy is currently being discussed [19, 20]. According to the WHO criteria, in

a population with optimal iodine supply the percentage of neonates with TSH values above 5 mIU/L is under 3% and increases to 3-19.9% in mild iodine deficiency, to 20-39.9% in moderate deficiency, and above 40% in severe iodine deficiency [5]. TSH values above 20 mIU/L (in Poland > 15 mIU/L) require recall of the infant for further examination to exclude congenital hypothyroidism [21-23]. In our group newborn TSH values (0.01-9.48 mIU/L) were within the normal range, and none of the children required re-examination. Surprisingly, hypothyroid women treated with L-thyroxine and iodine supplementation had children with 33% higher TSH values than those who did not receive iodine supplements, although the difference was not significant. Moreover, all of the neonates with TSH levels > 5 mIU/L were from mothers of the "thyroxine + iodine" group treated for overt hypothyroidism, without the residual functional thyroid tissue. It should be noted that none of the subjects took additional supplements containing iodine, and deliveries were conducted in departments that did not use iodine-containing disinfectants. Although, according to data from literature, the use of these substances results in an increase of TSH values above 5 mIU/L in 17.6% of neonates [24, 25], in our study their influence cannot be taken into account. Our findings could be explained by the inhibitory effect of iodine on foetal thyroid [26]. This kind of influence is especially marked in the iodine-deficient population, and is less pronounced when iodine supply is optimal [27]. Our data are inconsistent with some other studies indicating that increased frequency of elevated TSH values can serve as a marker of iodine deficiency [28]. We took into consideration the need to ensure the optimal iodine supply for pregnant women, as well as the consequences of iodine deficiency, especially for brain development of the foetus. However, in the group of hypothyroid women treated with L-thyroxine we did not show a positive influence of iodine supplementation on the foetal thyroid function parameter, which is the neonate TSH concentration. Similar results were obtained by other authors, who measured TSH concentrations in umbilical cord blood samples of children of healthy women receiving iodine supplementation in a dose of 150 µg daily [29]. Velasco et al. also found an increase of neonatal TSH in a group of pregnant women receiving 50-200 µg of iodine daily, but based on psychomotor tests performed at 3-18 months of age he also showed that iodine supplementation positively influenced on the neurological development of children [30]. However, recently these authors did not observe the positive impact of iodine supplementation during pregnancy on infant neurocognitive development [31], whereas Rebagliato et al. showed decreased psychomotor and mental index scores of infants in the first year of

life, whose mothers consumed ≥ 150 µg/day of iodine from supplements [32].

The vast majority of our subjects were women with autoimmune thyroid diseases. A limitation of our study was that we did not assess anti-TSH receptor binding antibodies, which could potentially cross the placenta and influence the foetal thyroids. Four of five children with TSH > 5 mIU/L were from women with Hashimoto's disease, and we cannot exclude a potential effect of anti-TSH blocking antibodies on the foetal thyroids. We also took into account the possible inhibitory effect of iodine on the foetal thyroid, however, there was no correlation between neonatal TSH concentrations and maternal median urinary iodine excretion. Moreover, the median ioduria in mothers of children with elevated TSH concentrations did not differ from the rest of the "thyroxine + iodine" group.

One of the most common causes of elevated neonatal TSH concentration is prematurity. In our group, 5 of 96 babies were premature (one from the "thyroxine" and four from the "thyroxine + iodine" group). Only one of them had TSH concentration > 5 mIU/L (5.66 mIU/L), while the TSH concentrations of the rest were within the range 0.51-3.86 mIU/L.

It should be expected that an extremely high dose of iodine may cause foetal hypothyroidism. The ability of foetal thyroid to escape the Wolff-Chaikoff mechanism as well as to avoid hypothyreosis is not entirely possible before 36 weeks of gestation [33]. The WHO recommendations estimate a daily dose of iodine above 500 µg to be excessive for pregnant women [4], while the US Institute of Medicine defines an upper limit in pregnancy on the level of 1100 µg per day [34]. Inclusion time of iodine supplementation as well as its beneficial effect on neurodevelopment of children is currently being discussed. Velasco et al. showed a positive effect of iodine supplementation starting at the 10th weeks of gestation [30], whereas Berbel et al. observed that iodine lost its favourable influence when implemented after the 10th week of pregnancy [35]. The group of Berbel treated with 200 µg iodine daily 92 women since 4-6 weeks of gestation, 102 women since 10-12 weeks of gestation, and 151 women after delivery. Based on the neurocognitive tests carried out at 18 months of age, those authors revealed a positive influence of this treatment on children's development only in a group supplemented since 4-6 weeks of gestation, and they did not find differences between the group supplemented since the 10th week of gestation and those not receiving supplementation during foetal life [35]. Liesenkortter et al. implemented 300 µg of iodine in 38 women since 10-12 weeks of pregnancy. Those authors compared the results with those of 70 non-treated women, and they did not show any difference in the neonatal TSH

concentrations [36]. It seems that the optimal dose of iodine, the strategy of its implementation in pregnant women at moderate iodine deficient areas, as well as the determination of the highest safe dose are still open questions. We realise that a limitation of our work is the small number of patients and the participation in the study of women both with overt and subclinical hypothyroidism. Women with partially preserved functional thyroid tissue frequently need lower increment of L-thyroxine dose during pregnancy than patients without functioning gland, which suggests that their residual thyroid cells may to a certain extent utilise iodine for thyroid hormone synthesis. However, the preliminary results encourage us to continue research work. It seems reasonable to extend the study and to separate the groups with overt and subclinical hypothyroidism, as well as to assess foetal/neonatal thyroid by ultrasound. We conclude that our results do not provide evidence of a positive influence of iodine supplementation on thyroid function of hypothyroid pregnant women sufficiently treated with L-thyroxine or their neonates. The results indicate the existence of iodine insufficiency in the population of Polish pregnant women, which might explain the particular sensitivity of foetal thyroid to the inhibitory effect of iodine.

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